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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,828	01/24/2002	**Xianqiang Li**	70-003300US	4192

22798 7590 07/08/2008

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1639	
MAIL DATE	**DELIVERY MODE**
07/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/057,828	LI ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed February 15, 2008 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Interview Request

3. Applicants request for an interview is acknowledged and granted. Please contact the examiner at the number indicated below to arrange a mutually beneficial time.

Status of the Claims

4. Claims 1-22 were pending. Applicants amended claims 1-22. No claims were added or canceled. Therefore, claims 1-22 are pending and examined on the merits.

Withdrawn Objections/Rejections

5. The Li et al. rejection under 35 U.S.C. § 102 is withdrawn in view of Applicants' amendments adding the "composition" limitation to all of the claims. All other rejections are maintained as set forth below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 103

6. Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kauffman et al. (WO 00/04196) (Date of Patent is **January 27, 2000**) (see 3/11/04 IDS) and Morris et al. (US Patent No. 6,458,530)(Filing Date is **April 4, 1996**) (of record).

For ***claim 1***, Kauffman et al. (see entire document) disclose "cis acting nucleic acid elements and methods of use" (e.g., see Kauffman et al., title and abstract), which renders obvious the claimed invention. For example, Kauffman et al. disclose a composition comprising a library of nucleic acid constructs each construct comprising a cis-element sequence comprising one or more copies of a cis element to which a specified transcription factor is known to bind (e.g., see claim 38, A plurality of isolated nucleic acid molecule [i.e., a library], each isolated nucleic acid molecule comprising one or more cis acting nucleic acid elements"; see also page 1, lines 29-30, "As an example, regulatory proteins called 'transcription factors' bind to cis acting nucleic acid elements"; see also see also page 2, line 5; see also page 14, last paragraph; see also page 9, paragraph 2; see also pages 5-6). Please note that Applicants' claims are drawn to a composition "comprising" a library of nucleic acid constructs and thus are open-ended. See MPEP 2111.03. That is, additional materials may be included in the composition including, for example, additional nucleic acids with cis-elements that are not known to bind to any known transcription factor. Interpreted as such, Kauffman et al. disclose many compositions interpreted here as "physical mixtures" (see *PIN/NIP, Inc. v. Platte Chemical Co.*, 64 USPQ2d 1344, 1350 (Fed. Cir. 2002) (""We therefore construe the term 'composition' ... to mean a physical mixture")) including, for example, mixtures in

equilibrium (e.g., see Kauffman et al., paragraph bridging pages 29 and 30, "For example, in one embodiment of the invention, nucleic acid binding factors bound to nucleic acids in a nucleic acid preparation are contacted [i.e., mixed] with a diverse population of isolated nucleic acids. The nucleic acid binding factors will equilibrate between being bound to the cis acting nucleic acid elements present in the nucleic acid preparation, and the cis acting nucleic acid elements present in the diverse population of isolated nucleic acid molecules."). Another example includes mixtures of protein/dna complexes retained after enzymatic digestion that only contain cis-elements that are known to bind to known transcriptions factors (e.g., see Kauffman et al., page 66, paragraphs 1 and 2, "Digestion of the bait DNA-nuclear protein complexes with such an enzyme selectively cleaves naked bait DNA and spares protein-complexed DNA … At this stage, the sets of selected bait DNAs are highly enriched in sequences that are capable of binding nuclear proteins and nuclear membrane receptors effectively [i.e., known to bind to transcription factors] … This yields a first crop of sequences among which known cis-elements are present"). Likewise, the elution of protein/dna complexes from a size exclusion column will also produce mixtures of the aforementioned DNA (e.g., see Kauffman et al., page 31, last paragraph, "nucleic acids bound to nucleic acid binding factors will pass through a chromatography column at a different rate than unbound nucleic acids [and thus be collected a mixture of bound nucleic acids]"). Finally, the isolated nucleic acids on a nitrocellulose filter or nucleic acid chip could also be considered as a "mixture" of resin/chip w/ the nucleic acid. Thus, Kauffman et al.

disclose the claimed compositions whether the claim is interpreted as only containing cis-element sequences to which specified transcription factor are known to bind or not. In addition, Kauffman et al. disclose that the cis element sequence varies within the library of nucleic acid constructs (e.g., see page 13, paragraph 1, "As an example, a population that includes all possible molecules of between 5 and 20 nucleotides in length, including each of the four naturally occurring nucleotides at each position, would have approximately ... 10^{13} different nucleic acid molecules. Such a population ... inherently includes all [i.e., known and unknown] possible cis acting nucleic acid elements of up to about 20 nucleotides in length"; see also page 8, first full paragraph; see also page 11, last paragraph; see also page 50, first full paragraph; see also page 22, paragraph 1, "The isolated nucleic acid molecules or the nucleic acid binding factors, or both ... can be biased populations that include cis acting nucleic acid elements ... that are known."). Please note that after a selection process as noted above (e.g., enzymatic digestion, elution from size exclusion column, etc.) only those sequences that bind to a transcription factor would be left. Kauffman et al. also disclose a promoter sequence 3' relative to the cis element sequence (e.g., see page 9, last paragraph, "A cis acting nucleic acid element can be localized within the nucleic acid sequence it regulates, or upstream or downstream thereof"; see also page 3, paragraph 1). Kauffman et al. also disclose a reporter sequence 3' relative to the promoter sequence (e.g., page 14, first full paragraph, "If desired, some or all of the isolated nucleic acid molecules can ... be flanked at one or both ends [i.e., both 3' and 5'] by ... detectable sequences [i.e., reporter molecules]"; see also paragraph

bridging pages 50-51, "… a plurality of isolated nucleic acid molecules containing cis acting nucleic acid elements can be … enhancers and promoters … or any other set of nucleic acid cis acting elements"). Finally, Kauffman et al. also disclose cis element sequences that "corresponds" to a given reporter sequence within the library of nucleic acid constructs (e.g., see page 14, first full paragraph; see also paragraph 19, lines 13-14; see also page 34, middle paragraph; see also page 35, paragraphs 1-3; see also page 60 paragraph 1 which disclose numerous methods of detection using reporter sequences that "correspond" to the cis element i.e., allow identification of the cis element).

For ***claims 2 and 3***, Kauffman et al. disclose the composition according to claim 1 wherein the reporter sequences comprise priming sequences 5' and 3' relative to the variable sequences including conserved sequences (e.g., see e.g., see page 14, first full paragraph, "If desired, some or all of the isolated nucleic acid molecules can include, or be flanked at one or both ends by, known sequences, such as sequences homologous to oligonucleotide primers for the polymerase chain reaction (PCR); see also page 25, last paragraph; see also page 33, first paragraph").

For ***claims 4-7***, Kauffman et al. disclose the composition according to claim 1 wherein the library comprises at least 100 different cis elements (e.g., see Kauffman et al. page 13, line 25 wherein 10^{13} different cis elements are disclosed).

For ***claims 8-10***, Kauffman et al. disclose the composition according to claim 1 with at least two copies of the cis element (e.g., see claim 38, "A plurality of isolated

nucleic acid molecules, each isolated nucleic acid molecule comprising one or more [i.e., two, three, four, etc.] cis acting nucleic acid elements"; see also page 57, lines 24-25).

For ***claims 11-13***, Kauffman et al. disclose the composition according to claim 1 with cis elements with a length between 5 and 50 base pairs (e.g., see page 10, first full paragraph, "A cis acting nucleic acid element is generally from about 4 to about 100 nucleotides in length, and is more typically from about 6 to about 25 nucleotides in length").

For ***claim 20***, Kauffman et al. disclose the composition according to claim 1 wherein different reporter sequences encode different reporter proteins (e.g., see page 3, paragraph 1; see also page 47, paragraph 1; see also column 6, paragraph 3, "see column 3, lines 46-53, "The methods are advantageous in providing a means for simultaneously identifying nucleic acid binding factors that modulate a genetic activity of a plurality of nucleic acids").

The prior art teaching of Kauffman et al. differs from the claimed invention as follows:

For ***claim 1***, the prior art teachings of Kauffman et al. differ from the claimed invention by not specifically reciting the use of a variable region within the reporter sequence nor does Kauffman et al. teach that each cis element sequence must correspond to a different reporter sequence within the library of nucleic acid constructs. Kauffman et al. only teach the use of the same reporter sequence.

For ***claims 14-19***, the prior art teachings of Kauffman et al. differ from the

claimed invention by not specifically reciting the size of the variable sequence in the reporter e.g., at least 14 bases in length (see claim 14).

For ***claims 21-22***, the prior art teachings of Kauffman et al. do not explicitly recite an "open reading frame" although it is undoubtedly implied from the molecular cloning techniques used i.e., the reporter wouldn't be expressed without it (e.g., see column 23, line 48).

However, Morris et al. teach the following limitations that are deficient in Kauffman et al.:

For ***claims 1 and 14-19***, Morris et al. (see entire document) disclose specially selected nucleic acid tags that contain different variable regions between 8 and 150 nucleotides in length for labeling molecular, cellular and viral libraries which would encompass the nucleic acid constructs of Kauffman et al. (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7). Morris et al. further disclose, in addition to the teachings noted above for Kauffman et al., that the tagged libraries may be in the form of a composition (e.g., see abstract, "Methods of selecting tag nucleic acids and VLSIPS^{TM} arrays and the arrays made by the methods are used to label and track compositions, including cells and viruses, e.g., in libraries of cells or viruses. In addition to providing a way of tracking compositions in mixtures, the tags facilitate analysis of cell and viral phenotypes."; see also field of invention; see also column 4, paragraphs 1-4; see especially column 2, second full paragraph, "For instance,

as explained herein, all of the members of a cellular library can be tested for response to an environmental stimulus using a mixture [i.e., a composition] of all of the members of the cellular library in a single assay. This is accomplished, e.g., by labeling each member of the cellular library, e.g., by cloning a nucleic acid tag into each cell type in the library, mixing each cell type in the library in an appropriate solution, and exposing part of the solution to the selected environmental stimulus."). Please note that the term "composition" has been held to represent a "physical mixture" by the Federal Circuit. See *PIN/NIP, Inc. v. Platte Chemical Co.*, 64 USPQ2d 1344, 1350 (Fed. Cir. 2002) (""We therefore construe the term 'composition' … to mean a physical mixture").

For ***claim 21***, Morris et al. disclose the use of open reading frames (e.g., see column 11, paragraph 3; see also example 1, especially column 24, lines 14-51).

For ***claim 22***, both Morris et al. and Kauffman et al. do not explicitly state that a stop codon is 3' relative to the reporters disclosed therein, but the Examiner contends that stop codons are typically used in the art and the reporter sequence would not have the proper length if it did not contain such a stopping point. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make and use the variable reporters as taught by Morris et al. with the cis acting nucleic acid library as taught by Kauffman et al. because Kauffman et al. explicitly state, "[n]ucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening procedures for identifying cis acting nucleic acid elements" (e.g., see Kauffman et al., column 16, lines 53-54), which would encompass the automated nucleic acid chips disclosed by Morris et al. i.e., the references represent analogous art (e.g., see Morris et al., figure 5 disclosing a nucleic acid chip). Furthermore, one of ordinary skill in the art would have been motivated to use the variable reporters as taught by Morris et al. because the variable reporters "provide a much more cost-effective approach to screening" (e.g., see Morris et al., column 11, lines 60-62) and facilitate "massive parallel analysis" (e.g., see Morris et al., Summary of Invention), which would improve upon the high throughput screening embodiments disclosed by Kauffman. In addition, less "ambiguities" would result in the high throughput screening assay when using the reporters disclosed by Morris et al. (e.g., see column 2, last paragraph and column 3, paragraphs 1-2, "In one class of embodiments, the invention provides a method of selecting a set of tag nucleic acids designed for minimal cross hybridization to a VLSIPS^{TM} array … because it reduces ambiguities in the interpretation of hybridization results which arise due to multiple nucleic acid species binding to a single species of probe on the VLSIPS^{TM} array"). Furthermore, one of ordinary skill in the art would have reasonably expected to be

successful because both Morris et al. and Kauffman et al. teach the use of "cloning" techniques to produce the nucleic acid libraries (e.g., compare Kauffman et al., page 50, last paragraph, "The plurality can be produced in abundance by, for example, chemical synthesis or by amplification by the polymerase chain reaction" to Morris et al., "Also, because the methods of using the arrays and tags optionally include PCR, LCR and other in vitro amplification techniques for amplifying tag nucleic acids, the kits of the invention optionally include reagents for practicing in vitro amplification methods such as taq polymerase"). Furthermore, Kauffman et al. explicitly state, "[n]ucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening procedures for identifying cis acting nucleic acid elements" (e.g., see Kauffman et al., column 16, lines 53-54), which would encompass the automated nucleic acid chips disclosed by Morris et al. (e.g., see Morris et al., figure 5 disclosing a nucleic acid chip).

Alternatively, the Examiner contends that the mere substitution of one reporter for another, which are both known in the art for labeling nucleic acids, would lead to the same predictable result in this case, namely, identification of the cis-elements. Thus, even if, *assuming arguendo*, Kauffman et al. did not provide motivation (which is not the case, see above) such a substitution would still be obvious in light of the Supreme Court *KSR* decision. *KSR Int'l Co. v. Teleflex Inc No.*, 550 U.S._____, 82 USPQ2d 1385, 1396 (S.Ct. Apr 30, 2007).

Response

7. Applicants' arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the reasons set forth below. Please note that the above rejection has been modified from its original version to more clearly address applicants' new arguments and claim amendments.

[1] Applicants argue, "The elements of the claim are not taught in Kauffman and Morris … e.g., the fact that "each construct" comprises a cis element that is "known to bind" to a 'specified transcription factor.'" (e.g., see 2/15/08 response, pages 6-8, especially page 8, paragraphs 2-4, more particularly paragraph 3).

[1] The Examiner respectfully disagrees. First, Applicants use open-ended "comprising" terminology which does not preclude the use of additional cis elements that are not "known to bind" in the mixture. That is, only the "library" need contain members with this requirement. Other substituents, including nucleic acids, in the mixture which are not considered to be "part of the library" can thus contain cis elements that are not known to bind. Thus, Applicants' arguments are not commensurate in scope with the claims. Further, even if, *assuming arguendo*, the claims could be fairly interpreted as suggested by Applicants Kauffman et al. disclose such a library. For example, when the library is digested with an enzyme, only the members "known to bind" are left behind (see Kauffman et al., page 66, paragraphs 1 and 2, "Digestion of the bait DNA-nuclear protein complexes with such an enzyme selectively cleaves naked bait DNA and

spares protein-complexed DNA … At this stage, the sets of selected bait DNAs are highly enriched in sequences that are capable of binding nuclear proteins and nuclear membrane receptors effectively [i.e., known to bind to transcription factors] … This yields a first crop of sequences among which known cis-elements are present). Likewise, the elution of protein/dna complexes from a size exclusion column would also produce the claimed mixtures (e.g., see Kauffman et al., page 31, last paragraph, "nucleic acids bound to nucleic acid binding factors will pass through a chromatography column at a different rate than unbound nucleic acids [and thus be collected a mixture of bound nucleic acids]").

[2] Applicants argue, "A teaching that a nucleic acid between 5 and 20 nucleotides in length of any combination of naturally occurring nucleotides, while technically including every possible nucleic acid of that length, is not sufficient to teach a particular subset of nucleic acids because it does not teach how or why one of skill would identify and select that subset, e.g., a group of cis acting sequences that each bind to a specified transcription factor as required in the claimed invention." (e.g., see 2/15/08 response, page 9, paragraph 2).

[2] Again, as noted above, Applicants' arguments are not commensurate in scope with the claims. Applicants' use of open-ended "comprising" terminology does not preclude additional sequences and thus would read on every possible nucleic acid. Further, enzymatic treatment or size exclusion chromatography as noted in response [1] and the above rejection would leave behind only those sequences that are known to bind. Consequently, contrary to

Applicants' assertions, the Kauffman reference does provide guidance on "how and why" one skilled in the art would identify, select and produce such a subset.

[3] Applicants argue, "Kauffman do not contain two corresponding variable regions" (e.g., see 2/15/08 response, page 9, last paragraph).

[3] In response to applicant's arguments against the Kauffman reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The combined references teach both as outlined in the above rejection.

[4] Applicants argue, "Morris does not teach two corresponding variable sequences" (e.g., see 2/15/08 response, page 10, paragraph 1).

[4] In response to applicant's arguments against the Morris reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The combined references teach both as outlined in the above rejection.

[5] Applicants argue, "The fact that one reference has a variable region in one nucleic acid and another reference teaches a variable region in an unrelated nucleic acid, both of which

are used in different ways cannot be combined to produce one nucleic acid with two variable regions that vary dependently or correspond to each other as claimed, e.g., to allow identification of cis acting elements and transcription factors." (e.g., see 2/15/08 response, page 10, paragraph 1).

[5] The Examiner respectfully disagrees. First, it is noted that is accusation is entirely unsupported in fact or reasoning. That is, Applicants merely state that this cannot be done without providing any rationale for making such an accusation. Second, Applicants' argument fails to appreciate that the sequences disclosed by Kauffman all contain tags for labeling the cis elements. Thus, the tags in Morris are merely be substituted for the tags in Kauffman for the reasons outlined in the rejection. As noted by the Supreme Court, there mere substitution of one component for another to produce predictable results (i.e., tagging) represents a prima facie case of obviousness. Thus, even if, *assuming arguendo*, Kauffman et al. did not provide motivation (which is not the case, see TSM analysis in above rejection) such a substitution would still be obvious in light of the Supreme Court *KSR* decision. *KSR Int'l Co. v. Teleflex Inc No.*, 550 U.S._____, 82 USPQ2d 1385, 1396 (S.Ct. Apr 30, 2007).

[6] Applicants argue, "The Office action appears to consider this a product by process claim and states that the product is the same and therefore it does not matter whether the transcription factors are specified beforehand ... Applicants respectfully disagree. Specifying which transcription factors the cis elements in the library recognize also leads to a different product; a library of nucleic acids known to bind to a particular group of transcription factors in

contrast to the library of Kauffman in which it is not known which constructs bind to transcription factors and if so, which transcription factors." (e.g., see 2/15/08 response, page 10, second to last paragraph).

[6] This is a product by process claim and, as stated previously, it does not matter whether the transcription factors are specified beforehand. For example, if a person of skill in the art would to "randomly" produce Applicants' claimed sequences (i.e., without prior knowledge of the transcription factors to which they would bind) the sequences would be identical in structure and thus would anticipate the claims. Thus, "prior knowledge" of the transcription factors to which the sequences bind is not required. Further, Applicants' use of open-ended comprising terminology does not preclude the use of additional sequences in the composition including sequences that would fail to bind any transcription factors at all. Finally, Kauffman et al. disclose "subsets" of sequences via enzymatic digestion, size exclusion chromatography, etc. (e.g., see above rejection, see also section [1] above) that are "known to bind" specific transcription factors and, in fact, provide methods for isolating and identifying the transcription factors that are bound.

[7] Applicants argue, "Furthermore, the Office argued that the reporters of Kauffman correspond to the cis element but they actually correspond to a randomized sequence - not to a specified transcription factor or cis element sequence. This is not correspondence as claimed, e.g., each different cis element corresponding to a different reporter." (e.g., see 2/15/08 response, page 10, last paragraph).

[7] In response to applicant's arguments against the Kauffman reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, Morris clearly teaches using the tags to "bar code" molecular libraries (e.g., see column 10, second to last paragraph, "Thus, the 'tag' nucleic acid functions in a manner analogous to a bar code label, and the VLSIPS^{TM} array of probes functions in a manner analogous to as a bar code label reader."). Thus, it is clear that when the tags of Morris are substituted for the tags of Kauffman each cis element will have a corresponding tag that is unique.

[8] Applicants argue, "The rejection completely fails to show the motivation needed to modify the library of Kauffman from a randomized library to a known library wherein each construct binds to a known transcription factor." (e.g., see 2/15/08 response, page 11, paragraph 2).

[8] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to use the variable

reporters as taught by Morris et al. because the variable reporters "provide a much more cost-effective approach to screening" (e.g., see Morris et al., column 11, lines 60-62) and facilitate "massive parallel analysis" (e.g., see Morris et al., Summary of Invention), which would improve upon the high throughput screening embodiments disclosed by Kauffman. In addition, less "ambiguities" would result in the high throughput screening assay when using the reporters disclosed by Morris et al. (e.g., see column 2, last paragraph and column 3, paragraphs 1-2, "In one class of embodiments, the invention provides a method of selecting a set of tag nucleic acids designed for minimal cross hybridization to a VLSIPS^{TM} array … because it reduces ambiguities in the interpretation of hybridization results which arise due to multiple nucleic acid species binding to a single species of probe on the VLSIPS^{TM} array"). In addition, the mere substitution of one reporter for another, which are both known in the art for labeling nucleic acids, would lead to the same predictable result in this case, namely, identification of the cis-elements. Thus, even if, *assuming arguendo*, Kauffman et al. did not provide motivation (which is not the case, see above) such a substitution would still be obvious in light of the Supreme Court KSR decision. KSR Int'l Co. v. Teleflex Inc No., 550 U.S._____, 82 USPQ2d 1385, 1396 (S.Ct. Apr 30, 2007).

[9] Applicants argue, "there would be no reason to combine a variable reporter with a randomized unknown library" (see 2/15/08 response, 2/15/08 response, page 11, paragraph 2).

[9] The Examiner respectfully disagrees. The idea of "bar coding" is not new. It allows a person to distinguish between different items that are expected to behave differently. Clearly a

person of skill in the art would have recognized, as did Kauffman, that there are many cis element sequences that behave differently (e.g., bind to different transcription factors) depending on the nature of the sequence. Thus, any tag that would enable a person of skill in the art to distinguish these sequences would be beneficial. That is exactly what Morris delivers. A person of skill in the art using the tags of Morris could track many different cis-element containing sequences in a library simultaneously. They could then amplify (using PCR) and sequence those sequences to "correlate" the function with the structure (compare Kauffman et al., page 50, last paragraph, "The plurality can be produced in abundance by, for example, chemical synthesis or by amplification by the polymerase chain reaction" to Morris et al., "Also, because the methods of using the arrays and tags optionally include PCR, LCR and other in vitro amplification techniques for amplifying tag nucleic acids, the kits of the invention optionally include reagents for practicing in vitro amplification methods such as taq polymerase"). Furthermore, Kauffman et al. explicitly state, "[n]ucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening proscedures for identifying cis acting nucleic acid elements" (e.g., see Kauffman et al., column 16, lines 53-54), which would encompass the automated nucleic acid chips disclosed by Morris et al. (e.g., see Morris et al., figure 5 disclosing a nucleic acid chip), which would read on the chips of Morris.

[10] Applicants argue, "The Examiner relied on a quote in Kauffman stating that, "nucleic acid chips and automated detection procedures are particularly advantageous in high-throughput screening procedures for identifying cis-acting nucleic acid elements." (emphasis added). The claimed invention relies on the existence of previously identified cis-acting nucleic

acid elements. Therefore, the quote cannot provide a motivation to produce the claimed invention." (e.g., see 2/15/08 response, page 11, last paragraph).

[10] "[T]here is no requirement that the prior art provide the same reason as the applicant to make the claimed invention" (see MPEP § 2144). Thus, "previous identification" is not required. Here, a person of skill in the art would be motivated to "bar code" the different members of the library as set forth by Kauffman using the techniques as set forth by Morris to facilitate massive parallel screening as set forth in the rejection above. Furthermore, the mere substation of one tag for another to yield predictable results represents a prima facie case of obviousness even in the absence of motivation as set for in the above rejection under *KSR*.

[11] Applicants argue, "The problem solved by any combination of Kauffman and Morris, e.g., how to identify cis elements, is not the same as the problem solved by the claimed invention" (e.g., see page 12, first full paragraph).

[11] See [9] above.

[12] Applicants argue, "The prior art, as discussed above, relates only to randomized libraries with no identified binding specificity. In contrast, the claimed invention relates to a library of nucleic acids specifically selected for their ability to bind to a specified transcription factor." (e.g., see 2/15/08 response, page 12, last three paragraphs, especially second to last full paragraph).

[12] It is respectfully submitted that Applicants' characterization of the prior art is inaccurate. Kauffman et al., for example, distinguish between those sequences that specifically bind to transcription factors from those that do not using, for example, enzymatic degradation, size exclusion chromatography, etc. Further, whether the cis-element/transcription factor relationship was established before the library was created or, alternatively, after the library was created is irrelevant because the structure of the library members would be the same in either case. That is, Applicants are claiming a product, not a method, and thus the only relevant question is whether the structure of those library members known or rendered obvious by the art differs from the currently claimed structures. Further, Applicants' use of open-ended "comprising" terminology would not preclude the use of additional "random" sequences in the mixture (whether they bind or not) as noted above.

[13] Applicants argue, "While most practioners in the art, e.g., those studying and using transcription factors, nucleic acid libraries, and the like, are quite skilled, there is still no reason for anyone to put the variable reporters of Morris into the randomized library of Kauffman." (e.g., see 2/15/08 response, page 13, last paragraph).

[13] See, for example, [10] above.

[14] Applicants argue, "The Action alleged that a reasonable expectation of success for the Kauffman and Morris combination exists because the mere substitution of one reporter for another would lead to the same predictable result, namely the identification of the cis elements. Applicants respectfully point out that the cis elements of the claimed library are already

identified … so Applicants question how such a result could be applicable to or provide an expectation of success for the claimed invention in which all cis-elements are already known" (e.g., see 2/15/08 response, page 13, last paragraph).

[14] A reasonable expectation of success need to be shown for the combination of Kauffman and Morris, not Kauffman/Morris and Applicants' specification. Thus, Applicants' argument is moot.

[15] Applicants argue, "The problem with the rejection is that the combination of Kauffman and Morris would yield a different type of library that could not be as successful a library as claimed." (e.g., see 2/15/08 response, page 13, last paragraph).

[15] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a "successful" library) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In addition, the context of the success to which Applicants refer is unclear.

[16] Applicants argue, "Applicants ask a simple question: which of the 10^{13} sequences of Kauffman are to be used with the reporters of Morris to provide a library specific to transcription factors as claimed? With no correspondence between particular cis-element/transcription factor

binding pairs and the variable reporters, the reporters of Morris serve no purpose for the libraries of Kauffman." (e.g., see 2/15/08 response, page 14, paragraph 1).

[16] To answer the question, each sequence in Kauffman would be tagged with a unique sequence as set forth by Morris (i.e., each sequence in Kauffman would be "bar coded" just like an item in the grocery store). The sequences would then be screened and, perhaps, physically separated (e.g., enzymatically degraded, separated using size exclusion chromatography, gel-shift assay, etc.). The sequences displaying the desired characteristics would then be "read" using the "bar code reader" (i.e., the array). Thus, the tags of Morris would allow "massive parallel screening" to occur for each unique cis-element containing sequence as set forth by Kauffman.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Claims Rejections – 35 U.S.C. 103

8. Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. (WO 00/34435) (Date of Patent is **June 15, 2000**) and Morris et al. (US Patent No. 6,458,530) (Filing Date is **April 4, 1996**) (of record).

For ***claim 1***, Li et al. (see entire document) teach cis-element reporter constructs and uses thereof including "high throughput" screening libraries (e.g., see abstract; see also example 4), which renders obvious the claimed invention. For example, Li et al. disclose a library of nucleic acid constructs (e.g., see figure 4A/B wherein a library of

"SEAP" constructs are disclosed including Ap1, HRE, Myc, p53, etc.). In addition, Li et al. disclose constructs comprising a cis-element sequence comprising one or more copies of a cis element to which a specified transcription factor is known to bind (e.g., see Li et al., pages 9-10, Example 1, The following cis elements were utilized for constructing cis-acting reporters: NF-kb … HRE … Myc … p53 … [etc.]"; see also page 10, last paragraph, "In a AP1-SEAP construct, the cis element in the construct contains six copies of AP1 … In a SRE-SEAP construct, the construct contains three copies of SRE element … [etc.]"). Li et al. also disclose that the cis element sequence varying within the library of nucleic acid constructs (e.g., see figure 4 A/B disclosing, for example, Ap1, HRE, Myc, p53, etc.). Li et al. also disclose a promoter sequence 3' relative to the cis element sequence (e.g., see Summary of Invention, "In one embodiment of the present invention, there is provided a cis element-reporter construct comprising a cis element, a reporter gene and a promoter"; see also figures 1-3 showing, for example, 3' orientation of the TK promoter relative to the KB4 cis element; see also Examples). Li et al. also disclose a reporter sequence 3' relative to the promoter sequence (e.g., see figures 1-3 showing SEAP, d2EGFP and luciferase reporters in a 3' position relative to the cis element, respectively; see also Examples). Finally, Li et al. disclose a "correspondence" between each cis element sequence and a given reporter sequence within the library (e.g., see figure 4A/B, wherein the amount of SEAP activity is shown to "correspond" to the type of cis element under various conditions).

For ***claims 4 and 5***, Li et al. disclose the composition according to claim 1

wherein the library comprises at least 20 different cis elements (e.g., see Example 2 and figure 4 wherein Li et al. disclose a library of 33 cis elements including 6 (AP1) + 3 (SRE) + 3 (CRE) + 3 (GRE) + 3 (HRE) + 4 (NF-kB) + 3 (NFAT) + 6 (myc) + 2 (p53)).

For ***claims 8-10***, Li et al. disclose the composition according to claim 1 wherein the cis element sequence comprises at least four copies of the cis element (e.g., see Example 2 and figure 4 A/B wherein the AP1 construct, for example, contains "six" copies).

For ***claims 11-13***, Li et al. disclose the composition according to claim 1 wherein an individual copy of the cis element has a length between about 5 and 50 base pairs (e.g., see Li et al., page 9, lines 6-7 wherein, for example, NF-kB with 40 base pairs is disclosed).

For ***claim 20***, Li et al. disclose the composition according to claim 1 wherein the different reporter sequences encode different reporter proteins (e.g., see figures 1-3 disclosing SEAP, d2EGFP and luciferase, respectively).

The prior art teachings of Li et al. differ from the claimed invention as follows:

For ***claim 1***, Li et al. fail to disclose a "composition" that comprises the library. Li et al. only disclose the use of "separate" library members transfected into different cell lines on microtiter plates (e.g., see Example 8, especially page 17, line 18 wherein 12 and 24 well plates are disclosed; see also Example 4, page 12, second to last paragraph, "Establishment of stable cell lines that express individual reporters expands application of this cis-element reporter in the cell-based high throughput drug screening.").

For ***claims 2-3***, Li et al. fail to disclose "priming sequences" 5' and 3' to the variable sequences.

For ***claims 6-7***, Li et al. fail to disclose a library with at least 50 cis elements. Li et al. only disclose a library of 33 cis elements.

For ***claims 14-19***, Li et al. fail to disclose the size of the variable sequence in the reporter.

For ***claims 21-22***, Li et al. fail to explicitly recite an "open reading frame" although it is undoubtedly implied from the molecular cloning techniques used i.e., the reporter wouldn't be expressed without it (e.g., see figures and Examples).

However, Morris et al. teach the following limitations that are deficient in Li et al.:

For ***claim 1***, Morris et al. (see entire document) disclose, in addition to the cumulative teachings noted above for Li et al, specially selected nucleic acid tags that contain variable regions between 8 and 150 nucleotides in length for labeling molecular, cellular and viral libraries which would encompass the nucleic acid constructs of Li et al. (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7). Thus, even if, *assuming arguendo*, Li et al. did not disclose this limitation (which is not the case, see above), this deficiency would be remedied by Morris et al. Morris et al. further disclose, in addition to the teachings noted above for Kauffman et al., that the tagged libraries may be in the form of a composition (e.g., see abstract, "Methods of selecting tag nucleic acids and VLSIPS^{TM} arrays and the arrays made by the methods

are used to label and track compositions, including cells and viruses, e.g., in libraries of cells or viruses. In addition to providing a way of tracking compositions in mixtures, the tags facilitate analysis of cell and viral phenotypes."; see also field of invention; see also column 4, paragraphs 1-4; see especially column 2, second full paragraph, "For instance, as explained herein, all of the members of a cellular library can be tested for response to an environmental stimulus using a mixture [i.e., a composition] of all of the members of the cellular library in a single assay. This is accomplished, e.g., by labeling each member of the cellular library, e.g., by cloning a nucleic acid tag into each cell type in the library, mixing each cell type in the library in an appropriate solution, and exposing part of the solution to the selected environmental stimulus."). Please note that the term "composition" has been held to represent a "physical mixture" by the Federal Circuit. See *PIN/NIP, Inc. v. Platte Chemical Co.*, 64 USPQ2d 1344, 1350 (Fed. Cir. 2002) (""We therefore construe the term 'composition' … to mean a physical mixture").

For ***claims 2-3***, Morris et al. disclose priming sites 5' and 3' to the reporter sequences (e.g., see figure 5 caption, "Tags were amplified using a single pair of primers that are homologous to the common priming sites which flank each tag [i.e., 5' and 3']").

For ***claims 6-7***, Morris et al. disclose "massive parallel analysis" (e.g., see Morris et al., Summary of Invention), which would render obvious larger numbers of constructs in order to "provide a much more cost-effective approach to screening" than the "12 or 24-well" approach disclosed by Li et al. (e.g., compare Morris et al., column 11, lines 60-62, "Even if the analysis were carried out in a parallel fashion using, e.g., 96-well plates,

the effort required to plate, organize, label and track each clone would be prohibitive. The present invention provides a much more cost-effective approach to screening cells" to Li et al., Example 8, "The activity assay of the present invention may be carried out in a 12 or 24 well plate"; see also column 4, first full paragraph, "In preferred embodiments, the set of tag nucleic acids comprises from 100-100,000 tags. Typically, a tag set will include between about 500 and 15,000 tags. Usually, the number of tags in a tag set is between about 5,000 and about 14,000 tags")

For ***claims 14-19***, Morris et al. disclose specially selected nucleic acid tags that contain variable regions between 8 and 150 nucleotides in length for labeling molecular, cellular and viral libraries that would encompass the nucleic acid constructs of Li et al. (e.g., see Morris et al., Summary of Invention; see also column 3, paragraphs 2-3; see also claim 7).

For ***claim 21***, Morris et al. disclose the use of open reading frames (e.g., see column 11, paragraph 3; see also example 1, especially column 24, lines 14-51).

For ***claim 22***, Morris et al. does not explicitly state that a stop codon is 3' relative to the reporters disclosed therein, but the Examiner contends that stop codons are typically used in the art and the reporter sequence would not have the proper length if it did not contain such a stopping point. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison

and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

It would have been *prima facie* obvious to of ordinary skill in the art at the time the invention was made to make and use the variable reporters as taught by Morris et al. with the cis acting nucleic acid libraries as taught by Li et al. because Morris et al. explicitly state that their sequences can be used to track, for example, recombinant cells in high throughput screening assays (e.g., see Morris et al., "This invention provides sets of nucleic acid tags, arrays of oligonucleotide probes, nucleic acid-tagged sets of recombinant cells …"), which would encompass the high throughput screening of recombinant cells disclosed by Li et al. (e.g., see Li et al., Example 4, "A set of d2EGFP reporters with different cis-elements were generated, which are used for monitoring different transcription factors. Establishment of stable cell lines that express individual reporters expands application of this cis-element reporter in the cell-based high throughput drug screening"; see also Example 5, "cell clones can be used in cell based high-throughput screening in search of factors involved in cAMP signal transduction pathway"). Furthermore, one of ordinary skill in the art would have been motivated to use the variable reporters as taught by Morris et al. because the variable reporters "provide a much more cost-effective approach to screening" than the "12 or 24-well" approach disclosed by Li et al. (e.g., compare Morris et al., column 11, lines 60-62, "Even if the analysis were carried out in a parallel fashion using, e.g., 96-well plates, the

effort required to plate, organize, label and track each clone would be prohibitive. The present invention provides a much more cost-effective approach to screening cells" to Li et al., Example 8, "The activity assay of the present invention may be carried out in a 12 or 24 well plate") and facilitate "massive parallel analysis" (e.g., see Morris et al., Summary of Invention), which would improve upon the high throughput screening embodiments disclosed by Li et al. In addition, less "ambiguities" would result in the high throughput screening assay when using the reporters disclosed by Morris et al. (e.g., see column 2, last paragraph and column 3, paragraphs 1-2, "In one class of embodiments, the invention provides a method of selecting a set of tag nucleic acids designed for minimal cross hybridization to a VLSIPS^{TM} array … because it reduces ambiguities in the interpretation of hybridization results which arise due to multiple nucleic acid species binding to a single species of probe on the VLSIPS^{TM} array"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because both Morris et al. and Li et al. teach general "cloning and expression" methods for both RNA and DNA that can used to create/track cellular libraries (e.g., see Morris et al., column 20, last paragraph, "Molecular cloning and expression techniques for making biological and synthetic oligonucleotides and nucleic acids are known in the art. A wide variety of cloning and expression and in vitro amplification methods suitable for the construction of nucleic acids are well-known to persons of skill"; see also column 8, line 29; see also column 9, last full paragraph; see also column 20, last paragraph; also Li et al., Summary of Invention, "In yet another embodiment of the present invention,

there is provided a method of monitoring activation of a transcription factor, comprising the steps of … transfecting a cell line with the vector; and detecting expression of the reporter gene, wherein expression of the reporter gene indicates activation of the transcription factor").

Response

9. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for reasons set forth below. Please note that the above rejection has been modified from it original version to more clearly address applicants' new arguments and claims.

[1] Applicants argue, "[We] herein amend the claims to clarify … that the constructs claimed are a part of a group in the same composition … The constructs of Li are not grouped together in this manner, nor would such a group be a successful because Li does not teach a correspondence between the various cis elements and reporters as claimed" (e.g., see 2/15/08 response, pages 14 and 15, especially page 15, first full paragraph).

[1] In response to applicant's arguments against the Li et al. reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the combined teachings of Li et al. and Morris et al. clearly teach the limitation of using a mixed composition as outlined

in the newly amended rejection above. For example, a person of skill in the art would realize that Morris et al. would facilitate "massive" parallel screening of mixtures via the "bar coding" techniques set forth therein. That is, a person of skill in the art could monitor multiple transcription factors simultaneous, say by mRNA (or corresponding cDNA) expression, and then "read" the cells that were so stimulated using the arrays set forth in Morris. This would represent a significant time saving advantage of the teachings in Li et al. who were monitoring these sequences (i.e., cloned into cell populations) individually on 12 and 24 microtiter plates.

[2] Applicants argue, "Morris does not teach two corresponding variable sequences" (e.g., see 2/15/08 response, paragraph bridging pages 15 and 16).

[2] In response to applicant's arguments against the Morris reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the combined references teach the claimed sequences as outlined in the rejection above.

[3] Applicants argue, "The fact that one reference has a variable region in one nucleic acid and another reference teaches a variable region in an unrelated nucleic acid, both of which are used in different ways cannot be combined to produce a group of nucleic acids, each with two variable regions that vary dependently or correspond to each other as claimed, e.g., to allow simultaneous identification of multiple transcription factors." (e.g., see 2/15/08 response, page 16, paragraph 1).

[3] The Examiner respectfully disagrees. First, it is noted that is accusation is entirely unsupported in fact or reasoning. That is, Applicants merely state that this cannot be done without providing any rationale for making such an accusation. Second, Applicants' argument fails to appreciate that the sequences disclosed by Li et al. all contain tags for labeling the cis elements. Thus, the tags in Morris are merely be substituted for the tags in Kauffman for the reasons outlined in the rejection (e.g., increase speed/amount of parallel screening). Further, as noted by the Supreme Court, there mere substitution of one component for another to produce predictable results (i.e., tagging) represents a prima facie case of obviousness. Thus, even if, *assuming arguendo*, Kauffman et al. did not provide motivation (which is not the case, see TSM analysis in above rejection) such a substitution would still be obvious in light of the Supreme Court *KSR* decision. *KSR Int'l Co. v. Teleflex Inc No.*, 550 U.S._____, 82 USPQ2d 1385, 1396 (S.Ct. Apr 30, 2007).

[4] Applicants argue, "There is nothing in Li or Morris to suggest or motivate the combination of references at issue." (e.g., see 2/15/08 response, page 16, paragraph 2).

[4] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to use the variable reporters as taught by Morris et al. because the variable reporters "provide a much more cost-effective approach to screening" than the "12 or 24-well" approach disclosed by Li et al. (e.g., compare Morris et al., column 11, lines 60-62, "Even if the analysis were carried out in a parallel fashion using, e.g., 96-well plates, the effort required to plate, organize, label and track each clone would be prohibitive. The present invention provides a much more cost-effective approach to screening cells" to Li et al., Example 8, "The activity assay of the present invention may be carried out in a 12 or 24 well plate") and facilitate "massive parallel analysis" (e.g., see Morris et al., Summary of Invention), which would improve upon the high throughput screening embodiments disclosed by Li et al. In addition, less "ambiguities" would result in the high throughput screening assay when using the reporters disclosed by Morris et al. (e.g., see column 2, last paragraph and column 3, paragraphs 1-2, "In one class of embodiments, the invention provides a method of selecting a set of tag nucleic acids designed for minimal cross

hybridization to a VLSIPS™ array … because it reduces ambiguities in the interpretation of hybridization results which arise due to multiple nucleic acid species binding to a single species of probe on the VLSIPS™ array").

[5] Applicants argue, "Because the constructs of Li do not have reporters that vary to provide each cis-element a different reporter, see, e.g., Figure 4, there would be no motivation to combine them into one composition, e.g., one that could be used to simultaneously identify multiple transcription factors in a single sample." (e.g., see 2/15/08 response, page 17, first full paragraph).

[5] See [1] and [4] above.

[6] Applicants argue, "As discussed above, the level of skill in the art is high. While anyone of skill in the art would be aware of the techniques needed to create each of the individual nucleic acids present in the claimed libraries, it is the combination that is novel and the Action has not stated any expectation of success that one of skill in the art would have had for such a combination. Therefore, one of skill would not have combined Li and Morris and had no expectation of success for doing so." (e.g., see 2/15/08 response, middle of page 17).

[6] The Examiner respectfully disagrees. As stated in the above rejection, one of ordinary skill in the art would have reasonably expected to be successful because both Morris et al. and Li et al. teach general "cloning and expression" methods for both RNA and DNA that can used to create/track cellular libraries (e.g., see Morris et al., column 20, last paragraph,

"Molecular cloning and expression techniques for making biological and synthetic oligonucleotides and nucleic acids are known in the art. A wide variety of cloning and expression and in vitro amplification methods suitable for the construction of nucleic acids are well-known to persons of skill"; see also column 8, line 29; see also column 9, last full paragraph; see also column 20, last paragraph; also Li et al., Summary of Invention, "In yet another embodiment of the present invention, there is provided a method of monitoring activation of a transcription factor, comprising the steps of … transfecting a cell line with the vector; and detecting expression of the reporter gene, wherein expression of the reporter gene indicates activation of the transcription factor"). Further, Applicants acknowledge that "the level of skill in the art is high." (see above).

Accordingly the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

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/Jon D. Epperson/
Primary Examiner, AU 1639